REMARKS

Reconsideration and allowance are respectfully requested.

Claims 34-57 are pending. The amendments clarify that the claimed invention are directed to expression vectors which transcribe a foreign gene different from the drug-resistance gene. New claims 46-47 do not require that the same promoter be used to express both the drug-resistance gene and the foreign gene. New claims 48-57 are duplicates of claims 36-45, except that they depend from either claim 46 or 47.

35 U.S.C. 112 – Written Description

Claims 34-45 were rejected under Section 112, first paragraph, because the Examiner alleged on pages 2-3 of the Office Action that they contain "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, the Examiner alleged that "the short-lived transcript drug-resistance genes are only described in the context of selecting cells comprising very specific expression constructs (e.g. construct A) integrated into the host cell genome for the purpose of preparing pre-packaging cells useful for the preparation of retroviral gene transfer vectors" (emphasis added, citations to Applicants' specification are deleted). Applicants traverse.

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). But the Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

In contradiction to the allegations made in the Office Action, Applicants' specification broadly describes use of a deteriorated drug-resistance gene, in contexts other than construct A and transfer into cell types other than packaging cells. Such description is explicit at several places in Applicants' specification, for example:

> [The present inventors] have also utilized the phenomenon that, in the preparation of the above-mentioned prepackaging cells, cells requiring the expression of a stronger resistance marker can be efficiently screened by using as a drug resistance marker gene one the function of which has been deteriorated by substitution, insertion or deletion in the base sequence in the coding region, one the translation efficiency of which has been lowered by substitution, insertion or deletion in the base sequence in the untranslated region (i.e., a low-efficient drug resistance gene), or one the stability of the mRNA produced by which has been lowered (i.e., a short-lived transcript drug resistance gene). In the present invention, use is made of these short-lived transcript drug resistance genes thus devised.

(pages 7-8 of the specification) This first teaching of Applicants demonstrates that their initial discovery of preparing prepackaging cells with constructs A and B was subsequently generalized to any cell type. The use of "a short-lived transcript drug-resistance gene" is not limited to gag/pol expressing cells (see pages 2-3 of the Office Action).

> As the drug resistance gene, use can be made of a neomycin resistance gene, a puromycin resistance gene, a hygromycin resistance gene, etc. which have been commonly employed in the art. Preferable examples thereof include a drug resistance gene the function of which has been deteriorated by substitution, insertion or deletion in the base sequence in the coding region thereof, a drug resistance gene the translation efficiency of which has been lowered by substitution, insertion or deletion in the base sequence in the untranslated region thereof (i.e., low-efficient drug resistance genes) and a drug resistance gene the stability of the mRNA produced by which has been lowered (i.e., a short-lived transcript drug resistance gene).

(pages 16-17 of the specification) This second teaching of Applicants is a description of "a short-lived transcript drug-resistance gene" in a general context. There is no limitation of their use to constructs A and B for the purpose of preparing prepackaging cells as alleged on page 3 of the Office Action.

> To more efficiently screen a stable cell line with a high expression level of the VSV-G gene product, therefore, the following DNA construction was devised and constructed.
>
> A short-lived mRNA sequence originating in c-fos was transferred into the 3'-untranslated region of a drug resistance gene to thereby reduce the productivity of the resistance gene, thus relatively efficiently screening a cell line with a high expression level from the CAG promoter. After transferring the Cre recombinase, the VSV-G gene was transcribed by the same promoter as the one for the resistance gene. Thus, it was expected that the

cell line screened by this DNA construction would have a high productivity of the VSV-G gene product.

(pages 36-37 of the specification) This third teaching of Applicants is a description of screening a stable cell line for high-level expression of a foreign gene like that for VSV-G protein which is transcribed from the same promoter as a short-lived transcript drug-resistance gene. There is no limitation to use of constructs A and B for the purpose of preparing prepackaging cells as alleged on page 3 of the Office Action.

Applicants taught in their specification, in general, that cells requiring expression of a stronger resistance marker can be obtained from a drug-resistant gene in which the mRNA transcript has been destabilized. A cell line having a high expression level of a foreign gene product (e.g., VSV-G protein) was actually obtained by transfer of the expression vector into cells, drug selection of the cells, and expressing a foreign gene product by the same promoter as the one for the resistance gene. This is the invention being claimed in this application; only claims 40 and 45 are limited to prepackaging cells.

Claims 35-40 were rejected under Section 112, first paragraph, because the Examiner alleged on page 4 of the Office Action that the phrase "wherein said expression vector confers drug resistance when transfected into a cell and the drug-resistance gene is transcribed at a higher rate under selection with the drug because of the presence of the mRNA-destabilizing sequence" is not supported by the specification as originally filed. Applicants traverse because the challenged limitations would be recognized as explicitly and implicitly described in the original disclosure by a person of ordinary skill in the art.

A device disclosed in the specification that inherently performs a function or has a property, operates according to a theory, or has an advantage necessarily discloses that function, theory, or advantage even though the specification says nothing explicit about the characteristic. See *In re Smythe*, 178 USPQ 279, 285 (C.C.P.A. 1973). An amendment introducing an inherent characteristic of such a device into the claims is not prohibited by the written description requirement. See *id.*

As noted above, Applicants' specification teaches use of an expression vector for a foreign gene comprising a short-lived transcript drug-resistance gene, in which the same promoter transcribes the foreign gene and the drug-resistance gene. Page 37 of the specification explicitly teaches drug selection of cells into which the expression vector was transferred.

In addition, high-rate transcription by the promoter due to the presence of the mRNA-destabilizing sequence is implicit in the teaching of such drug-selected cells. As admitted on page 4 of the Office Action, "The specification provides support for *selection* from a larger population of cells." As Applicants have discussed in reference to the three portions of their specification and the other Section 112 rejection, selection of cells is not limited to prepackaging cells. Furthermore, it is implicit in their use of mRNA-destabilizing sequences that the promoter transcribing the drug-resistance gene and the foreign gene is activated by insertion in the cell's genome. The promoter is activated to transcribe at a high rate to compensate for destabilization of the short-lived transcript of the drug-resistance gene. Only the cell with this promoter survives. This is consistent with the admission on page 9 of the Office Action, "Differences in gene expression for the constructs taught in the specification appear to be due to the location of insertion of the targeting vector in the specification and not due to some structural aspect of the claimed vector itself" (emphasis added).

Therefore, Applicants submit that their explicit and implicit teachings provide an adequate written description of the claimed invention. Also submitted for consideration is a copy of Li et al. (J. Virol. 74:6564-6569, 2000) which shows that a retrovirus is not required to use Applicants' invention. Li et al. use pCALNdLG which is a vector originally disclosed in this application (see pages 21-22 of the specification and Fig. 2).

Withdrawal of the written description rejections made under Section 112, first paragraph, is requested because the specification conveys to a person skilled in the art that Applicants were in possession of the claimed invention as of the filing date.

35 U.S.C. 103 – Nonobviousness

To establish a case of prima facie obviousness, all of the claim limitations must be taught or suggested by the prior art. See M.P.E.P. § 2143.03. Obviousness can only be established by combining or modifying the prior art teachings to produce the claimed invention if there is some teaching, suggestion, or motivation to do so found in either the references themselves or in the knowledge generally available to a person of ordinary skill in the art. See, e.g., *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992). It is well established that the mere fact that references can be combined does not render the resultant combination obvious unless the desirability of that combination is also taught or suggested by the prior art. See *In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990). Thus, even if all elements of the claimed invention were known, this is not sufficient by itself to establish a prima facie case of obviousness without some evidence that one would have been motivated to combine those teachings in the manner proposed by the Examiner. See *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (B.P.A.I. 1993).

Evidence of the teaching, suggestion or motivation to combine or to modify references may come explicitly from statements in the prior art, the knowledge of a person of ordinary skill in the art or the nature of the problem to be solved, or may be implicit from the prior art as a whole rather than expressly stated in a reference. See *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); *In re Kotzab*, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000). Rigorous application of this requirement is the best defense against the subtle, but powerful, attraction of an obviousness analysis based on hindsight. See *Dembiczak* at 1617. Whether shown explicitly or implicitly, however, broad conclusory statements standing alone are not evidence because the showing must be clear and particular. See *id.*

It should be noted that an unexpected advantage is provided by Applicants' invention: a highly expressed clone is obtained with expression of a foreign gene directed thereby. The portions of Applicants' specification quoted above teach that a drug-resistance gene with deteriorated function (e.g., short-lived transcript) can be used

to obtain stronger expression of the resistance marker. This situation can be exploited by directing strong expression of a foreign gene product (e.g., VSV-G protein). Notwithstanding the Section 103 rejections below, such results demonstrate that the claimed invention is not obvious.

Claims 34-38 and 41-43 were rejected under Section 103(a) as allegedly unpatentable over Pavlakis et al. (U.S. Patent 5,972,596) in view of DePonti-Zilli et al. (Proc. Natl. Acad. Sci. USA 85:1389-1393, 1988). Applicants traverse because, although it was alleged on page 7 of the Office Action that Pavlakis et al. have suggested that the neomycin resistance gene would be an effective reporter in their system, actually this suggestion is absent from the disclosure of the '596 patent. To determine whether putative regulatory sequences are sufficient to confer mRNA stability control, DNA with a suspected inhibitory/instability sequence (INS) is fused to an indicator or reporter gene to create a gene which is transcribed as a hybrid RNA. Col. 13, lines 13-17, of the '596 patent. Neomycin is listed as an example of the indicator or reporter gene. Col. 13, lines 19-21, of the '506 patent. But no expression vector with a functional drug-resistance genes is disclosed by Pavlakis et al. and there is no motivation given in the '596 patent for substituting neomycin as the indicator or reporter in the expression vectors disclosed by Pavlakis et al. It was also admitted in the Office Action that DePonti-Zilli et al. do not teach that the ß-actin gene-*neo* mRNA levels were controlled primarily by transcriptional processes and not by changes in mRNA stability (i.e., they did not teach that their expression vector has an mRNA-destabilizing sequence).

The Examiner proposes on page 8 of the Office Action that the combination of these references would have been motivated "to characterize the ability of a putative transcriptional regulatory sequence to affect the stability/utilization of a neomycin resistance gene transcript." This is an inadequate basis for a case of prima facie obviousness. Pavlakis et al. list several different indicator or reporter genes, including a neomycin resistance gene. There is no suggestion in either reference for selecting the neomycin resistance gene over any of the other listed indicator or reporter gene if the

objective is merely to characterize a suspected INS. Certainly DePonti-Zilli et al. were not successful in showing that an mRNA-destabilizing sequence could be characterized using such expression vectors. Furthermore, it was neither taught nor suggested by the cited references that an expression vector with a drug-resistance gene having or linked to an mRNA-destabilizing sequence could be used to select for high-level expression of a foreign gene in drug-resistant cells as the claimed invention is able to do.

Furthermore, in contradiction to the assertion made on pages 8-9 of the Office Action, it should be noted that the location of insertion of the expression vector in a cell is a structural difference between the claimed invention and Schuler et al. The latter describe cells which transiently express *neo* and were never selected by the drug. Therefore, the cells of Schuler et al. do not resemble Applicants' cells because there would be no expectation that the vector of Schuler et al. insert at locations which result in high rates of expression.

Therefore, it is submitted that no evidence has been presented in the Office Action that one of ordinary skill in the art would have been motivated to make the combination proposed by the Examiner because there is no teaching or suggestion for using a neomycin resistance gene instead of any other indicator or reporter gene to characterize a suspected INS.

Claims 34-38 and 41-43 were rejected under Section 103(a) as allegedly unpatentable over Pavlakis et al. (U.S. Patent 5,972,596) in view of Gritz et al. (Gene 25:179-188, 1983). Applicants traverse for reasons similar to those stated above.

Pavlakis et al. does not teach an expression vector with a drug-resistance gene. Like DePonti-Zilli et al., Gritz et al. teach a drug-selectable expression vector with a drug-resistance gene (hygromycin) but it is not used to characterize a suspected INS.

The Examiner proposes on page 10 of the Office Action that the combination of these references would have been motivated "to easily assay for protein encoded by the hybrid transcripts comprising the putative INS sequence, as taught by Pavlakis et al, by either enzymatic means or by direct genetic selection, as taught by Gritz et al." This is an inadequate basis for a case of prima facie obviousness. Pavlakis et al. list several

different indicator or reporter genes, but it does not appear that there is any description of a hygromycin resistance gene. Nor is there any suggestion in either reference for selecting the hygromycin resistance gene over any of the other listed indicator or reporter gene if the objective is merely to characterize a suspected INS. Certainly Gritz et al. were not concerned with characterizing an mRNA-destabilizing sequence. Furthermore, it was neither taught nor suggested by the cited references that an expression vector with a drug-resistance gene having or linked to an mRNA-destabilizing sequence could be used to select for high-level expression of a foreign gene in drug-resistant cells as the claimed invention is able to do.

Furthermore, in contradiction to the assertion made on pages 10-11 of the Office Action, it should be noted that the location of insertion of the expression vector in a cell is a structural difference between the claimed invention and Schuler et al. The latter describe cells which transiently express *neo* and were never selected by the drug. Therefore, the cells of Schuler et al. do not resemble Applicants' cells because there would be no expectation that the vector of Schuler et al. insert at locations which result in high rates of expression.

Therefore, it is submitted that no evidence has been presented in the Office Action that one of ordinary skill in the art would have been motivated to make the combination proposed by the Examiner because there is no teaching or suggestion for using a hygromycin resistance gene instead of any other indicator or reporter gene to characterize a suspected INS.

Claims 34-38 and 41-43 were rejected under Section 103(a) as allegedly unpatentable over Pavlakis et al. (U.S. Patent 5,972,596) in view of de la Luna et al. (Gene 62:121-126, 1988). Applicants traverse.

Pavlakis et al. does not teach an expression vector with a drug-resistance gene. Like DePonti-Zilli et al., de la Luna et al. teach a drug-selectable expression vector with a drug-resistance gene (puromycin) but it is not used to characterize a suspected INS.

The Examiner proposes on page 12 of the Office Action that the combination of these references would have been motivated "to easily assay for protein encoded by the

hybrid transcripts comprising the putative INS sequence, as taught by Pavlakis et al. by either enzymatic means or by genetic selection, as taught by de la Luna et al." This is an inadequate basis for a case of prima facie obviousness. Pavlakis et al. list several different indicator or reporter genes, but it does not appear that there is any description of a puromycin resistance gene. Nor is there any suggestion in either reference for selecting the puromycin resistance gene over any of the other listed indicator or reporter gene if the objective is merely to characterize a suspected INS. Certainly de la Luna et al. were not concerned with characterizing an mRNA-destabilizing sequence. Furthermore, it was neither taught nor suggested by the cited references that an expression vector with a drug-resistance gene having or linked to an mRNA-destabilizing sequence could be used to select for high-level expression of a foreign gene in drug-resistant cells as the claimed invention is able to do.

Furthermore, in contradiction to the assertion made on pages 12-13 of the Office Action, it should be noted that the location of insertion of the expression vector in a cell is a structural difference between the claimed invention and Schuler et al. The latter describe cells which transiently express *neo* and were never selected by the drug. Therefore, the cells of Schuler et al. do not resemble Applicants' cells because there would be no expectation that the vector of Schuler et al. insert at locations which result in high rates of expression.

Therefore, it is submitted that no evidence has been presented in the Office Action that one of ordinary skill in the art would have been motivated to make the combination proposed by the Examiner because there is no teaching or suggestion for using a puromycin resistance gene instead of any other indicator or reporter gene to characterize a suspected INS.

Withdrawal of the Section 103 rejection is requested because the invention as claimed would not have been obvious to a person of ordinary skill in the art at the time it was made.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 34-38 and 41-43 were rejected under Section 102(b) as allegedly anticipated by Schuler et al. (Cell 55:1115-1122, 1988). Applicants traverse.

It was alleged on page 15 of the Office Action that Schuler et al. necessarily disclose expression vectors. This is incorrect because expression vectors are known to express a foreign gene different from the drug-resistance gene. Applicants' claimed invention requires that the expression vector ultimately express the foreign gene, but there is neither teaching nor suggestion in Schuler et al. of nondrug-resistance genes. Furthermore, Schuler et al. do not select cells with a drug and it is not clear that the cells transfected in accordance with their procedure (see page 1121 of the reference headed "Transfer and Transient Expression of Recombinant Genes") are drug resistant.

Withdrawal of the Section 102 rejection is requested because all limitations of the claimed invention are not disclosed by the cited reference.

Having fully responded to all of the pending objections and rejections contained in the Office Action (Paper No. 21), Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect.

Respectfully submitted,

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